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Monograph

Sacubitril and valsartan fixed combination to reduce heart failure events in post-acute myocardial infarction patients

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Summary

Heart failure is a term used to define a constellation of symptoms and signs that are commonly attributed to the inability of the heart to produce a cardiac output that meets the demands of the body. It remains a deadly disease, affecting between 1-2% of the population, and is more common in the elderly, with around 6-10% of patients over 65 suffering from the condition. Sacubitril/valsartan (LCZ-696) is a combined neprilysin inhibitor and angiotensin AT_1 receptor blocker approved in recent years for the treatment of chronic heart failure with reduced ejection fraction. In an area where there have been limited pharmacological advances in the last 10 years, this drug was

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a game changer and a much welcomed addition to contemporary heart failure therapy. It is currently being studied in patients with heart failure with preserved ejection fraction and for the reduction of heart failure events post-acute myocardial infarction. Results from the ongoing PARADISE-MI study are awaited by the global cardiology community with great interest.

Key words: Sacubitril/valsartan – LCZ-696 – Heart failure – Myocardial infarction

Background

Heart failure is a term used to define a constellation of symptoms and signs that are commonly attributed to the inability of the heart to produce a cardiac output that meets the demands of the body. Exertional dyspnea, peripheral edema as well as orthopnea are the usual findings following history taking and physical examination. It remains a deadly disease and increasingly effective treatments in modern day medicine mean that patients are living longer and are more likely to have multiple comorbidities when they present to hospital. It affects between 1-2% of the population and is more common in the elderly; around 6-10% of patients over 65 years of age suffer from the condition (1).

The term "heart failure with reduced ejection fraction" and "heart failure with preserved ejection fraction" describe two completely different diseases and underlying pathophysiology. Around 50% of patients with heart failure have preserved ejection fraction. However, in day to day clinical practice, unless explicitly stated otherwise, the use of the term heart failure is commonly understood to refer to heart failure with reduced ejection fraction. The reduction in systolic function of the left ventricle commonly results from a variety of causes. This is also dependent on geographical location and prevalence of other environmental risks such as communicable diseases, malnutrition and low socioeconomic status. In North America and Western Europe, coronary artery disease remains the biggest underlying cause of heart failure with reduced ejection fraction (HFrEF). While in Africa and Asia, rheumatic heart disease is still a major cause, similar to the role played by hypertension in the African-American cohort (2).

Physiological Consequences of Heart Failure

A reduction in ejection fraction activates a sequence of adaptive mechanisms to maintain adequate cardiac output. The renin–angiotensin–aldosterone system (RAAS) as well as the adrenergic system are activated which leads to increased left ventricular contractility and vasoconstriction. The resulting increase in sodium and water retention, heart rate and blood pressure synergistically aim to maintain adequate cardiac output. Although this neuroendocrine activation initially aims to meet cardiac output demand, continuous activation results in maladaptive cardiac remodeling and has deleterious effects on left ventricular function (3). The circulating levels of angiotensin-2 (Ang II) have been shown to increase in heart failure, impacting on cell function and altering intrinsic myocardial contractility, ventricular stiffness and diastolic function (4). Meanwhile, continuous sympathetic drive has been shown to result in eccentric left ventricular hypertrophy, maladaptive remodeling and worsening heart failure (4). High circulating aldosterone levels were found to have an impact on cardiac function. This occurs through mechanisms such as magnesium/potassium loss, sympathetic activation, parasympathetic inhibition and also myocardial fibrosis (5, 6).

Contemporary Heart Failure Therapy

Based on the above hypotheses, multiple randomized controlled trials have been conducted over the last three decades to investigate and establish treatment for heart failure. Blockade of the adrenergic, as well as the RAAS, formed the basis of therapy. ß-Blockers have been shown in trials such as CIBIS-II, COPERNICUS and MERIT-HF to reduce mortality by up to a third (7-9).

Almost a decade earlier, CONSENSUS and SOLVD investigators also confirmed the mortality benefit of angiotensin-converting enzyme (ACE) inhibitors when added to standard heart failure therapy (10, 11).

Despite treatment with ACE inhibitors and the progress that was made, mortality from heart failure remained high. The concept of "aldosterone escape" led researchers to test the hypothesis of aldosterone antagonists to improve heart failure mortality (12). This led to the design of the RALES trial which sought

to answer this question with the drug spironolactone. The trial was stopped early due to marked mortality benefit in the spironolactone arm (13).

The Role of Natriuretic Peptide and Neprilysin Inhibition

The natriuretic peptide system counteracts the effects of RAAS activation, inhibits secretion of arginine vasopressin and modulates the autonomic nervous system (14). The release of brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) promotes natriuresis and vasodilatation and occurs as a response to the resulting increase in ventricular preload and afterload seen in heart failure (14). In the atrium, atrial natriuretic peptide (ANP) is also released as a response to atrial stretch and plays a similar role to BNP and NT-proBNP.

Naturally, efforts have been made to try and manipulate this pathway to improve heart failure outcomes. Initial strategies have focused on two aspects: the administration of exogenous natriuretic peptide as well as the inhibition of its breakdown. BNP and NT-proBNP are broken down by neprilysin, a membrane bound endopeptidase. Disappointingly, the administration of the recombinant BNP nesiritide in the ASCEND-HF study, which was a large randomized, double-blind, placebo-controlled trial, did not show any mortality benefit nor did it reduce the rate of heart failure hospitalizations.

Early attempts at neprilysin inhibition with the hope of raising the levels of natriuretic peptide and its activity unmasked another factor that had to be considered. Compounds such as racecadotril and candoxatrilat, although successful in raising levels of ANP, did not produce a sustained hemodynamic effect that was desired (14). It soon became apparent that due to the role that neprilysin also plays in Ang II breakdown, lone neprilysin inhibition without concurrent inhibition of the RAAS was not likely to succeed due to persistent circulating levels of Ang II (14). The vasodilatory effects obtained were offset by the vasoconstriction caused by Ang II.

Chemical Structure, Pharmacokinetics and Metabolism

Sacubitril/valsartan (LCZ-696) is a combined neprilysin inhibitor and angiotensin AT_1 receptor blocker. Its empirical formula (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na_3$ 2.5 H_2O with a molecular mass of 957.99. The chemical structure is shown in Figure 1.

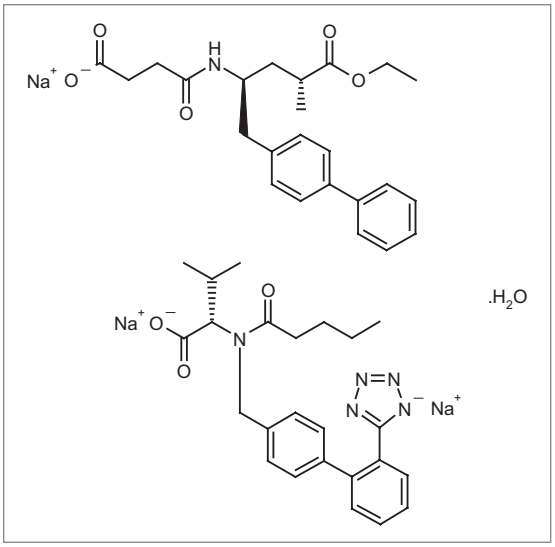

Figure 1. Chemical structure of sacubitril/valsartan (LCZ-696).

Sacubitril is a prodrug and the therapeutic effect of sacubitril/valsartan is partly achieved via the action of the active metabolite of sacubitril, LBQ-657, which inhibits neprilysin. At the same time, blockade of the Ang II type 1 (AT_1) receptor is provided by the action of valsartan and it is this concurrent inhibition of both pathways that leads to sacubitril/valsartan's overall therapeutic effect (Fig. 2).

In a study involving 30 selected patients who were given the drug in dosages of 100 mg twice daily and 200 mg twice daily, plasma concentrations of sacubitril, LBQ-657 (sacubitrilat) and valsartan increased rapidly and reached plasma concentration within 0.5, 2.5 and 2 h, respectively (15). C_{max} and $AUC_{0\text{-}12h}$ for sacubitril and LBQ-657 were dose-proportional while for valsartan they were less so (15).

Levels of cyclic guanosine monophosphate (cGMP) in the urine and plasma as well as levels of ANP in the urine were increased in volunteer subjects. Plasma renin markers (plasma renin activity, plasma renin concentration) were significantly raised during the same period. All of these biomarker trends reflect neprilysin inhibition and AT_1 receptor blockade (15).

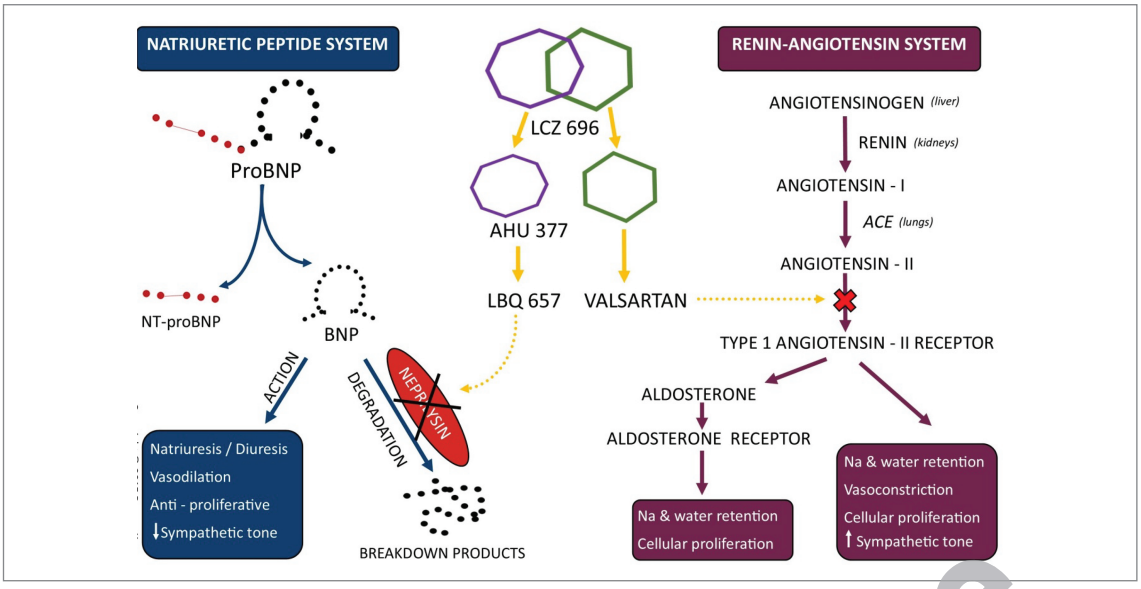

Figure 2. Mechanism of action for sacubitril/valsartan (LCZ-696).

Oral bioavailability is estimated to be around at least 60%. The terminal half-lives of sacubitril, LBQ-657 and valsartan have been 1.3, 12 and 21 h, respectively (16). Steady state levels of sacubitril/valsartan with a twice-daily dosing regimen are achieved in 3 days.

Drug elimination is primarily through renal excretion in the form of the active metabolite LBQ-657. An estimated 51-68% is excreted through the urine while the remainder is excreted through the feces. In vivo studies have demonstrated a low risk of inhibiting or inducing the cytochrome P450 (CYP) enzymes (16).

Clinical Studies

PARAMOUNT and PARADIGM-HF

The PARAMOUNT study was a phase II, randomized, parallel-group, double-blind multicenter trial in patients with New York Heart Association (NYHA) class II-III symptoms and heart failure with preserved ejection fraction (HFpEF). This was defined as having an ejection fraction of more than 45% and NT-proBNP > 400 pg/mL (17). Patients were assigned to receive either sacubitril/valsartan, titrated to 200 mg twice daily or valsartan, titrated to 160 mg twice daily. The trial was designed to investigate the safety and efficacy of sacubitril/valsartan in patients with HFpEF. The primary endpoint was change from baseline in the levels of NT-proBNP at 12 weeks (17). Secondary endpoints measured were echocardiographic parameters, blood pressure, NYHA class and quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) (17, 18). Although the initial change in NT-proBNP was significant at 12 weeks in the sacubitril/valsartan group, this was no longer significant at 36 weeks. Despite an improvement in NYHA class, there was no significant difference in echocardiographic parameters or quality of life (17, 18). Whether some of these positive signals will translate into improved outcomes is unclear and currently a prospective trial (PARAGON-HF) is ongoing to address this question (ClinicalTrials.gov Identifier NCT01920711).

The PARADIGM-HF trial was another trial designed to compare the effects of sacubitril/valsartan to those of enalapril in patients with HFrEF. It was a double-blind trial and 8,442 patients with NYHA class II-IV symptoms and an ejection fraction of at least 40% were randomized to either sacubitril/valsartan (at a dose of 200 mg daily) or enalapril (at

a dose of 10 mg twice daily), in addition to recommended therapy (19).

The primary outcome was a composite of death from a cardiovascular cause or hospitalization for heart failure (19). There was an overwhelming mortality benefit in the sacubitril/valsartan arm and the trial had to be stopped early. The primary outcome had occurred in 914 (21.8%) of the patients who received sacubitril/valsartan, compared to 1,117 (26.5%) of the patients who received enalapril (hazard ratio = 0.80 in the sacubitril/valsartan group; 95% confidence interval: 0.73 to 0.87; $P < 0.001$) (19).

The most frequent adverse effect seen in the study was hypotension, which was more common in patients given sacubitril/valsartan. However, this did not cause a significant number of patients to discontinue the drug as there were only 36 patients (0.9%) in the sacubitril/valsartan group and 29 (0.7%) in the enalapril group who had to discontinue the drug because of hypotension.

Hypotension is a risk factor for renal failure and although this has been a concern, the study findings suggest lower incidents of clinically relevant increases in serum creatinine and drug discontinuation in the sacubitril/valsartan arm (18, 19). Similarly, event rates for angioedema were reassuringly low, unlike findings from earlier studies of neprilysin inhibition such as the OVERTURE study where angioedema was found to be higher in the omapatrilat group compared to the enalapril group (20). This result is likely attributed to sacubitril/valsartan not inhibiting ACE or aminopeptidase P, two enzymes known to be involved in bradykinin breakdown, which was the Achilles' heel of omapatrilat (18, 19). A similarly notable observation is the incidence of hyperkalemia that occurred more frequently in the enalapril group where 236 (5.6%) patients had a serum potassium of more than 6 mmol/L compared to the sacubitril/valsartan group which only saw 181 (4.3%) patients with the same adverse side effect (19).

What is also worth noting in the PARADIGM-HF study is the higher proportion of patients on contemporary heart failure therapy. This is in contrast to earlier heart failure trials and reflects modern day practice. More than 90% of patients were on a β-blocker, at least 80% were on a diuretic, and more than half were on a mineralocorticoid antagonist (19). Despite what is perceived to be optimum medical therapy, sacubitril/valsartan still offered significant mortality benefit above and beyond standard treatment. These findings are compelling and have indeed begun to change the landscape of chronic heart failure treatment.

The Future: PARADISE-MI

Currently, sacubitril/valsartan is indicated for patients who remain symptomatic despite being on optimum heart failure therapy, including an optimum dose of an ACE inhibitor. This can be defined as having a hospital admission for heart failure exacerbation or worsening symptoms in an outpatient setting.

The next logical step, however, is to investigate whether sacubitril/valsartan could be used at an earlier stage, prior to the use of an ACE inhibitor in patients who have suffered a myocardial infarction and therefore are at risk of heart failure. The early hemodynamic changes postinfarction resulting from stimulation of the sympathetic nervous system, RAAS, and release of ANP and BNP often leads to deleterious left ventricular remodeling. Sacubitril/valsartan has already proven itself to be more influential than conventional ACE inhibitors in altering the course of chronic heart failure patients. It is hoped that earlier intervention in the myocardial remodeling process postinfarction will translate into better outcomes for patients.

The Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) aims to answer this clinical question and is currently recruiting and the study is expected to be completed in 2020. It is a multicenter, randomized, double-blind, controlled trial and will evaluate the effect of sacubitril/valsartan titrated to a target dose of 200 mg twice daily against ramipril titrated to a target dose of 5 mg twice daily in patients following a myocardial infarction, on top of standard postmyocardial infarction treatment.

Primary outcome will be a composite endpoint of cardiovascular death, heart failure hospitalization and outpatient heart failure (time-to-first-event analysis) with evidence of left ventricular systolic impairment or pulmonary congestion

with no previous history of chronic heart failure (ClinicalTrials.gov Identifier NCT02924727). With such promising results from PARADIGM-HF, it is hoped that PARADISE-MI will further offer clinicians treatment options to reduce the incidence of heart failure in postmyocardial infarction patients and reduce cardiovascular mortality.

Conclusions

Sacubitril/valsartan is opening up a wealth of opportunities for patients with HFrEF. In an area where there has been limited pharmacological advances in the last 10 years, this is a game changer and a much welcomed addition to contemporary heart failure therapy. The clinical data is robust, and the drug has been proven to offer marked mortality benefit over ACE inhibitors in chronic heart failure patients with a good drug safety profile. Its use in patients with HFpEF is unclear as phase II trial data to date have not shown significant difference with standard therapy.

Whether sacubitril/valsartan will change outcomes in the postmyocardial infarction cohort who are at risk of developing heart failure remains to be seen, and results from PARADISE-MI will be awaited by the global cardiology community with great interest.

Disclosures

The authors state no conflicts of interest.

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